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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/568,649

02/16/2006

Giorgio Terenghi

TEPH 109

4566

23579

7590

08/25/2010

Pabst Patent Group LLP

1545 PEACHTREE STREET NE

SUITE 320

ATLANTA, GA 30309

EXAMINER

WANG, CHANG YU

ART UNIT

PAPER NUMBER

1649

MAIL DATE

DELIVERY MODE

08/25/2010

PAPER

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RECORD OF ORAL HEARING
UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte GIORGIO TERENGHI, PARI-NAZ MOHANNA and
DAVID P. MARTIN

Appeal 2009-012878
Application 10/568,649
Technology Center 1600

Oral Hearing Held: July 22, 2010

Before ERIC B. GRIMES, LORA M. GREEN and JEFFREY N. FREDMAN,
Administrative Patent Judges

ON BEHALF OF THE APPELLANT:

PATRICIA PABST, ESQ.
Pabst Patent Group
1545 Peachtree Street, NE
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Atlanta, Georgia 30309

1 THE USHER: Good morning. Public Calendar Number 37, Appeal Number
2 2009-012878, Appellant Giorgio Terenghi, Pabst Patent Group, LLP.

3 JUDGE GRIMES : Good morning.

4 MS. PABST: Good morning. And this is Dr. David Martin.

5 He's one of the inventors from the assignee of the company. He's going to
6 talk in just a minute., a very brief introduction, unless we appreciate the
7 opportunity to be here and have a chance to discuss some of the issues.

8 What I'd like to do is let Dr. Martin talk for three or four minutes,
9 just to generally talk about the technology, why the developed it amongst any
10 problem in the field, and why do you suppose they were so unexpected. And
11 then I'm going to talk about the legal errors that occurred in this case.

12 DR. MARTIN: Hello. I'm David Martin. I'm the VP of R&D at
13 Tepha and I've been working with PHAs, which is a class of materials that we
14 manufacture at Tepha for almost 20 years now. We started manufacturing
15 these materials by cloning genes and putting them into microorganisms, so we
16 created a cell that can function as a chemical engineering factory to make
17 these polymers.

18 Originally, there was one polymer, poly3hydroxybutyrate that
19 was used and there was extensive work done on that in the area of
20 implantation, but it was found to be too crystalline, too stiff and slow
21 absorbing to be useful in the late 90s when we first created this P4HB
22 material. It was the first time it had ever been made and after testing amyls
23 found that it could be useful for medical implants. It took us over 10 years to
24 get the first medical device cleared through the FDA as a suture, and now
25 we're beginning commercialization of a variety of medical implants based on

1 that material.

2 In early 2000 we started work on nerve guides with an expert in
3 the field in the UK, Giorgio Terenghi, who had previously done work with the
4 P3HB material and found that it didn't quite work as rapidly as would be
5 necessary. So I created a foam of our new material, P4HB, that had pores in it
6 and it could be rolled into a flexible tube, a hollow tube, to allow axonal
7 growth across a nerve gap. And, originally when the experiment was set up,
8 we picked end points of 10 and 20 days to observe the progression of nerve
9 growth across the gap and unexpectedly, at the first explanation time point of
10 10 days the axon had already cleared the gap and this was much faster than he
11 had previously observed with the other observable polymer, P3HB.

12 So that's when we knew we had found some interesting and
13 unexpected results. And then we had followed, at later time points, with
14 histology and observed the quality of nerve growth and subsequently filed a
15 patent based on those findings. So there's been review papers published
16 subsequent to that that suggest absorbable nerve guides are useful, and this
17 type of application. But I don't think people have observed as quite as fast
18 axonal regrowth as we observed in our initial studies. So at Tepha we're
19 continuing to commercialize these materials and have been focusing on
20 mostly tissue regeneration and wound closure devices. And now I'll try to
21 commercialize that into that technology into a variety of different
22 applications.

23 JUDGE GRIMES: Thank you.

24 MS. PABST: Again, what I'm going to do is just take a couple
25 of minutes to go over what I think are some legal errors, and then if there are

1 any questions or issues. I think the first, major legal error that occurred in this
2 case is that the examiner refused to consider the evidence. There are two
3 actual groups of evidence.

4 The first is that in the application as filed we have a discussion of
5 the prior art; and, in particular, we have a paper that was submitted in an
6 information disclosure statement. And the examiner made it of record, and
7 then when we cited this paper as showing comparative evidence, the examiner
8 said she would not consider it even when in our reply brief we again
9 established where this paper had been made of record.

10 JUDGE GRIMES: Which paper are you referring to?

11 MS. PABST: That is the Hazizi et al. paper.

12 JUDGE GRIMES: The Hazari reference?

13 MS. PABST: The "British Journal of Plastic Surgery;" the
14 reason this paper was particularly important, it's cited in the application.

15 JUDGE GRIMES: I'm sorry. This is Hazari, British Journal of?

16 MS. PABST: Plastic Surgery.

17 JUDGE GRIMES: Plastic surgery. Okay. Thank you.

18 MS. PABST: Yes. Volume 52, 1999, the authors of this paper
19 include one of the inventors of this application, and that's Dr. Terenghi. This
20 is the work that Dr. Martin just discussed with respect to the P3HB. In the
21 application as filed we reference this paper and provide a summary of the
22 results. Now, there were two differences between the material that is
23 described in this paper and in what is claimed. The first is that that paper
24 used P3HB, and we claim P4HB or P4HB copolymer.

25 Second, none of the prior art, but in particular the nerve tube

1 used and described in this paper was porous, and this claim "porous P4HB
2 nerve guide." So we have two differences that in the materials that were used
3 in the two studies. The studies with the porous P4HB nerve guide are
4 described in the application in example 5 at pages 9 to 10. So we think it was
5 legal error that the examiner refused to consider the closest prior art, which
6 was the P3HB without pores, and P4HB with pores, and the results.

7 If one reads the paper and the example, not only do we have a
8 common inventor and author, but in fact it is the identical animal model and
9 conditions used for the two situations: the rat's severed sciatic nerve, neural
10 tube put in place, and then the results that she think compared. What was
11 surprising to everybody was the fact that if you look at the papers cited by the
12 examiner, these are subsequent reviews. And this is another thing she found
13 to consider.

14 She cited two papers as being subsequent reviews. Clavijo
15 Alvarez in the PRS Journal, "Plastic Reconstructive Surgery Journal," and she
16 cited Schlosshauer -- and I don't know how to pronounce these names. I
17 apologize -- in the "Journal of Neurosurgery." And both of them say that
18 there was a need to have nerve guides that could encourage neuronal
19 regeneration that approached that of an allograft and then all of the synthetic
20 guides had to fail to reach that goal. That included the P3HB of Hazizi. So
21 we have in the application as filed evidence that shows that in fact this nerve
22 guide made of P4HB and porous can achieve that rate of axonal regeneration.

23 We show that by the first time, 10 days, we had already seen
24 nerves completely close this gap. That had never been observed in any
25 synthetic nerve guide prior to this example. It approaches the rate of an

1 allograft for nerve regeneration. In the field of nerves and in all of the papers
2 cited by the examiner show this, that that rate of neuronal regeneration is
3 critical to outcome.

4 We have longstanding, as established by the evidence the
5 examiner cited, we have unexpected results here because we see axonal
6 regeneration approaching that of an allograft. There is no prior art that gives
7 you any indication that you could achieve that. If I am a patient who has had
8 severed nerve, and particularly if it's a fairly long gap, that rate of
9 regeneration is critical.

10 Now, there are other errors that we think the examiner made.
11 Not only did the examiner refuse to consider the evidence of record, but a
12 number of misstatements are made with respect to the references that she
13 cited. I actually went through, as I'm sure you all have done, because neither
14 tests this, gone through and looked at the places where she cites support for a
15 number of her statements about what's shown in the prior art. And, I have to
16 be honest. I have never seen this before.

17 The references she cites simply do not support her statements.
18 She makes statements that are not only unsupported but they were
19 contradicted by the passages that she actually cites, which is unusual. To give
20 you an example, she makes reference to "Neuro Tube," which is one of the
21 prior art nerve regeneration guides, which is also discussed in her reviews.
22 And she says it shows a porous neuro tube. It does not show a porous neuro
23 regeneration tube. It shows a material having microparticles in the material.
24 That's not a pore. It's a micro particle. It is the antithesis of what we claim.

25 If you take the material that we're claiming, lay it on a napkin

1 and pour fluid on top, the fluid will pass through, important self regeneration.
2 It allows free diffusion of those nutrients and gas to support the viability of
3 that nerve cell. If you take a solid material, it does not. Having micro-
4 particles in that structure may provide benefits since it's collagen and BCM.
5 But it does not allow free diffusion. So not only is it not the same, it doesn't
6 achieve the same goal.

7 So we have a number of differences there. We have no prior art
8 showing a porous nerve tube. Now, when one looks at the prior art that was
9 cited, in particular, Tepha's own earlier applications, there is a clear teaching
10 that P4HB is a wonderful polymer. There's no dispute. And that there's a
11 long list of materials that we might believe we make out of this. But those
12 materials, such as the nerve guides, are not porous. There's no disclosure in
13 any prior art reference of a porous nerve guide.

14 In fact, there's a teaching away, because they are solid polymers,
15 the tubes. They are not porous materials. So even if you put all that prior art
16 in combination, you would not have a P4HB porous nerve guide. You would
17 have a teaching away from it. Now, one of the reasons for this is because
18 those polymers don't have the mechanical properties of P4HB. So I think,
19 again, we have prior art that doesn't disclose each claimed element. We have
20 unexpected results. We have longstanding, but unmet, need. I think every
21 one of these are the criteria the Supreme Court laid out in "John Deere" and
22 "KSR" for non-obviousness. And I think we have legal error by the examiner
23 in refusing to consider the evidence showing those things.

24 JUDGE GRIMES: I don't read the examiner as having not
25 considered your evidence of unexpected results. She says that it's not

1 persuasive because it's not a side-by-side comparison.

2 MS. PABST: Well, first off, the examiner is incorrect in that
3 statement, because in fact it was done by the same person with the same
4 animal model under the same conditions, the examiner never looked at.
5 However, I believe that if you looked at what the examiner actually says in
6 her, it's hard to take and know what the examiner is saying, because she starts
7 out with why she won't consider the evidence.

8 And then when she gets to the end, she says, well, it's not the
9 same. The reason she says it's not the same is because she did not in fact read
10 the evidence before her. We had two interviews in this case with the
11 supervisor present, and he encouraged her to look at the evidence.

12 JUDGE GRIMES: Okay. Well, we have the evidence and they
13 are similar experiments.

14 MS. PABST: They actually were done under the same
15 conditions with the same model. And I know that I'm not going to --

16 JUDGE FREDMAN: When was this? They're not exactly the
17 same. There's a little bit of everything.

18 MS. PABST: Well, the materials are different, but it was the
19 same. Dr. Terenghi performed the experiments described in the Blue Book by
20 Hazizi using a rat sciatic model and with a ten millimeter.

21 JUDGE FREDMAN: But you're giving us information that is in
22 the record. At least it's not clear that Dr. Terenghi exhibited both of them
23 himself. For the record, I don't think that -- says that.

24 MS. PABST: Well, I don't think there's any requirement, but the
25 legal requirement that the same person do the studies. It is the same animal

1 model. It is the same size gap. It is the same general concept. The materials
2 are clearly different. That's, of course, the whole point.

3 JUDGE GRIMES: Our problem here is that even if it's the same
4 experiment that is being done by different people at different times, you might
5 get somewhat different results.

6 MS. PABST: Well, in fact, by virtue it being an animal model,
7 you can never have identical conditions. I think the standard is what do those
8 skilled in the art think of those results. This was not a single example as you
9 can see from Example 5 in the application.

10 Several different forms of these materials were tested across the
11 board with the porous P4HB made under four different conditions. You see
12 the same results. They are statistically, significantly, better than what is in
13 any of the prior art, even in the reference cited by the appellants here Hazizi et
14 al., or in any of the reviews cited by the examiner, which are later in date to
15 applicant's work.

16 If you look at, for example, Ms. Schlosshauer that she cites, here
17 is the 2007 part, 2006 paper. So three years after our prior art where they
18 review all of these materials, and they don't even come close to achieving the
19 results achieved by the appellants with their material using four different
20 samples, multiple rat models. So, yes, there are some differences, but across
21 the board it is statistically, significantly better. It meets that longstanding
22 need, and it's the same animal model. And, if you look at Schlosshauer, who
23 is one of probably far greater than ordinary skill in the art, in his review he
24 feels very comfortable comparing results with far greater animal models in
25 drawing these conclusions.

1 JUDGE GRIMES: And you made the point earlier that the goal
2 was to get an artificial material that would replicate or that would approach
3 the rate of regeneration of an axonal graft. Is that correct?

4 MS. PABST: Of an allograft.

5 JUDGE GRIMES: An allograft?

6 MS. PABST: Yes. That is the standard Schlosshauer.

7 JUDGE GRIMES: And the result in your specification, they
8 don't include the results from the autologous nerve graft control. But it is
9 those who understand --

10 MS. PABST: It's not a control. It's in the literature.

11 JUDGE GRIMES: No. It's not in the spec as well, and the
12 results are presented for the P4HP sample, but they're not compared to the
13 autologous nerve graft. I'm reading from the specification.

14 JUDGE FREDMAN: But we receive autologous nerve grafts.

15 MS. PABST: Right.

16 JUDGE FREDMAN: In our graft, right?

17 MS. PABST: Yes.

18 JUDGE FREDMAN: So that data is not presented.

19 JUDGE GRIMES: So my question to you is the expectation that
20 those autologous nerve graft animals would have bridged the gap at the 10-
21 day mark when the P4HB?

22 DR. MARTIN: Yes, it's possible that an allograft or an
23 autologous graft could achieve that, but there are disadvantages with using --
24 especially autologous graft -- because that needs to be harvested from the
25 patient. And so you suffer morbidity at the site and you might lose feeling.

1 So there are disadvantages to using autologous nerve grafts. And with
2 allografts you always have the possibility of disease transmission because it's
3 coming from another human.

4 So the move in the industry is to use a synthetic material where
5 you don't have these other disadvantages and achieve the same axonal
6 regeneration as the gold standard, which would be those autologous or
7 allografts.

8 JUDGE GRIMES: All right.

9 MS. PABST: I don't think in our case. I don't think we've ever
10 claimed it was the same. I think we used language like approaching. And the
11 point is compared to the prior art it's almost a log factor better.

12 JUDGE FREDMAN: The other question I had is you recognized
13 that your was better.

14 MS. PABST: I'm sorry. I'm having a little trouble hearing you.

15 JUDGE FREDMAN: The other question that I have is your
16 claim, Claim 1 in particular, it seems that it encompasses not just a
17 hydroxybutyrate, but also copolymers.

18 MS. PABST: It does.

19 JUDGE FREDMAN: So is it commensurate in scope with the
20 results, which are limited, for hydroxybutyrate?

21 MS. PABST: Well, as I pointed out in my reply brief, to the
22 extent the examiner never raised that as an issue. If it were raised, we do have
23 our Claim 3, where we had tried to correct it upon the examiner would enter
24 it. But again Claim 3 is limited to the homopolymer. And so if that had been
25 raised as an objection, which it wasn't, we felt that Claim 3 addressed that.

1 So, and actually, to be honest, we would be happy with that, because that is
2 what is being developed clinically and commercially. Because best results are
3 with the homopolymer, that is what the FDA has approved.

4 As Dr. Martin was saying, the first synthetic polymer approved
5 by the FDA in like 20, 30 years was the P4HB. So the FDA recognized that
6 this was a very special polymer and that's what's actually being developed.
7 So we wouldn't have a problem with that.

8 JUDGE GRIMES: I think we understand your position, or the
9 unmarked -- of that.

10 MS. PABST: Thank you, so much.

11 Whereupon, at 9:23 a.m., the proceedings were concluded.
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